placed in Category IIIA, the Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

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Generic Statement

Cholera Vaccine

Asiatic cholera is an acute diarrheal disease caused by *Vibrio cholerae*, which in its severe form is characterized by a massive loss of fluid and electrolytes. If untreated, this disease may result in circulatory collapse and death within 1 day. In reality, such severe cases are the exception rather than the rule, and epidemiological data indicate thart for each severe case there are 25 to 100 mild to asymptomatic cholera infections. For the most part, significant epidemics are limited to areas with poor sanitation. The possible appearance of imported cases of cholera in countries with good sanitation is enhanced by transportation and increased international travel. Since 1960, the seventh recorded pandemic of cholera has extended westward from Southeast Asia across the Indian Subcontinent, the Middle East, into the African Continent, and into portions of Southern Europe. A small outbreak of cholera occurred in Louisiana in late 1978.

It is now well-established that the disease is produced by a heat labile enterotoxin produced by *Vibrio cholerae* multiplying within the small bowel.

Infection follows the ingestion of water or food contaminated with human excretions containing *Vibrio cholerae*.

Highly satisfactory treatment of severe cholera is available consisting of prompt and adequate replacement and subsequent maintenance of fluid and electolyte losses and correction of metabolic acidosis. Adjunctive antibiotic therapy (usually with tetracycline) results in faster elimination of the organism and shortens the period of diarrhea. With prompt and adequate treatment, using intravenous and/or oral regimens, mortality is less than 1 percent. Unfortunately, adequate supplies of proper intravenous fluids and knowledge of treatment are often unavailable.

Immunization with cholera vaccine has been practiced for over 75 years, but no adequately controlled studies defining its relatively limited effectiveness were conducted until 1963. In the United States, the principal use of cholera vaccine is for military personnel and for individuals traveling to countries where cholera is endemic and/or where evidence of immunization is required. Although cholera is a quarantinable disease, under international health regulations, international certificates of vaccination for travelers from infected areas are no longer required in the United States and many other countries. In spite of the international health regulations and the total lack of any evidence that cholera vaccine prevents individuals from becoming carriers, some countries still require evidence of vaccination of travelers. The United States does not require vaccination of travelers from any country, and it is generally recommended that areas faced with an epidemic should not rely solely on vaccination but devote resources to provision of adequate treatment facilities, disease surveillance efforts, and improvment of sanitation.

Nature of Product

Cholera vaccine, as licensed in the United States, is a bivalent whole cell bacterial suspension containing equal quantities of Ogawa and Inaba serotypes of *Vibrio cholerae* at a concentration of 8×10^9 bacteria per mL. Only Ogawa and Inaba organisms of the "classical" biotype are employed since animal and field experience has shown that there is no advantage to the inclusion of organisms of the currently pandemic "El Tor" biotype that are antigenically identical and belong to either the Ogawa or Inaba serotypes.

Production

Organisms of the two serotypes are grown separately on agar, or in the case of one manufacturer, in a casein-hydrolysate broth. The bacterial count is standardized usually by opacity determination prior to addition of 0.5 percent phenol. The two serotype antigens are combined in equal amounts and diluted in 0.5 percent phenolized saline to a suspension of 8×10^9 organisms per mL for the final vaccine.

Although 0.5 percent phenol is the only killing-preserving agent currently employed in licensed vaccines, formalin, mild heat, and organic mercurials also have been employed in other countries. No clear-cut advantage or disadvantage of any particular killing-preserving agent is descernible form available data in man.

The final vaccine is tested according to the U.S. standards. In addition to tests for sterility and general safety, the vaccine must be tested for nitrogen content, freedom from toxicity (weight gain in mice), and antigenicity (protective activity in mice challenged intraperitionally with each serotype suspended in mucin).

Use and Contraindications

This product is intended for active immunization against cholera. Primary immunization of adults has traditionally consisted of two subcutaneous or intramuscular injections of 0.5 and 1.0 mL respectively, given 1 week to 1 month apart. Reduced doses have been recommended for children 10 years of age or under. Booster doses are recommended every 6 months as long as the likelihood of infection exists.

In the light of published data now available (Ref. 1), no advantage is gained by the 1.0 mL volume for the second dose, and the recommended schedule can be restated as follows:

Dose number	Dose volume (mL)			
	Intradermal[1] age (years) >5	<5	5–10	>10
1	0.2	0.2	0.3	0.5
2	0.2	0.2	0.3	0.5
Boosters	0.2	0.2	0.3	0.5

[1] Higher levels of protection (antibody) may be achieved in children <5 years by the subcutaneous or intramuscular routes. In adults, somewhat lower levels of protection may be obtained by the intradermal route, but this route may be used as a means of minimizing reactions where a high level of protection is not necessary (e.g., most foreign travelers).

Absolute contraindications to the use of cholera vaccine are virtually nonexistent. Severe reactions have been reported but are extremely rare. As with other antigens, individuals receiving corticosteroids or other immunosuppressive drugs may not display an optimum response. Immunization should be withheld during febrile illnesses to avoid confusion as to the cause of further fever.

Safety

Immunization with cholera vaccine is generally accompanied by mild to moderate tenderness at the injection site, although more severe local reactions may occur occasionally. Such reactions may persist 2 to 3 days.

Local reactions may be accompanied in some instances by mild fever, malaise, and headache. With adherence to the U.S. standards, excessive antigen content (i.e., significantly more than 8×10^9 organisms per mL) should be largely eliminated as a cause of potential reactions.

Each batch of cholera vaccine must pass the standard Bureau of Biologics requirements for safety before it is released.

In summary, untoward reactions are not a major problem with cholera vaccine when properly produced and administered.

Effectiveness

Properly controlled field trials of cholera vaccines were first conducted in the early 1960's. Over subsequent years a series of field trials have been carried out in Bangladesh, the Philippines, and India (Ref. 2). A variety of vaccines, some experimental, have been tested and their apparent efficacy has varied widely, as have results from one trial to another. In general, protection in the range of 30 to 90 percent has been observed and has persisted for 3 to 6 months. However, in a recent study a monovalent vaccine of higher potency has shown good protection for as long as 3 years.

The seasonal nature of cholera complicates evaluation of the duration of protection, but protection is minimal or nonexistent with most vaccines in the subsequent cholera season (i.e., usually 1 year later). More prolonged protection has been observed in trials of an experimental oil adjuvant vaccine in the Philippines and with a fluid vaccine of high antigen content in Bangladesh. The oil adjuvant vaccine produced severe local reactions in the majority of recipients.

Field trials of monovalent vaccines in Bangladesh and the Philippines have shown that primary immunization with the Ogawa vaccine gave no protection against Inaba infection, whereas Inaba vaccine offered some cross-protection against Ogawa infection. These studies validate the need for bivalent vaccine because the infecting serotype often cannot be predicted.

Although no precise correlation can be established between potency as determined in the mouse and human effectiveness in field trials, a general relationship seems to exist (Ref. 3). The mouse protection test shows the same trend in cross-protection between serotypes as observed in field trials. The ability to stimulate vibriocidal antibody in children is reasonally well correlated with vaccine potency determined in the mouse (compare Figures 3 and 4 (Ref. 3)). With bivalent vaccines, protection in man is correlated with acquisition of circulating vibriocidal antibody. Monovalent Ogawa vaccine stimulates vibriocidal antibody against the Inaba serotype, but fails to protect against Inaba infection, except perhaps in adults in endemic areas.

Therefore, the mouse protection test seems to be the most reasonable potency assay now available, although the disease in the mouse, a fulminating septicemia, bears no resemblance to cholera in man.

Although the vaccine prevents clinical cholera in approximately 50 percent of recipients for 3 months or longer, cost-effectiveness data indicate that cholera vaccination is of little value as a public health measure in combating a threatened cholera epidemic. Cholera vaccines do not interrupt transmission or prevent acquisition of the carrier state. It seems wiser to expend resources to improve diagnosis, to make available simple rehydration facilities (which are needed regardless of vaccination), to improve surveillance, to conduct health education programs, and, where possible, to improve sanitation. Unfortunately, few health authorities can resist the intense political and public clamor for mass vaccination programs which at best will offer limited protection to only a small segment of the population at risk, even in the rare instances when they can be efficiently carried out.

Special Problems

The major limitation of immunization against cholera with presently available vaccines is their inability to induce an efficient and durable immunity in the gut. Parenteral immunization does not seem to be an efficient means of stimulating the secretory immune system against cholera. Oral immunization with killed vaccines or live avirulent vaccine is a current research objective.

Recognition of the fact that *Vibrio cholerae* induces disease by production of a potent heat-labile enterotoxin (which is a classical exotoxin) has raised extensive interest. This antigen is not present in significant quantities in any available vaccine. A highly purified toxoid, detoxified with glutaraldehyde (because formalin-toxoid showed reversion), has failed to confer significant protection when administered parenterally in field trials in Bangladesh and the Philippines. It is possible that this antigen combined with the whole cell vaccine may have additive or synergistic effects, but this awaits future product development and field trial. Oral administration of toxoid is also being considered, in the hope of inducing secretory antibody. This assumes great importance, because available data from animal models clearly indicate the need for neutralization of the toxin before it can act on epithelial cell surfaces lining the gut.

Recommendations

1. The Panel recommends that public support for development of an improved cholera vaccine should be continued. Such support is necessary because unsatisfactory sanitary conditions in many countries, including some in the Western Hemisphere, make it clear that control of the disease by sanitation alone cannot be realized in the foreseeable future.

2. Due to limited effectiveness of presently available vaccines, the Panel does not recommend that they be employed as a primary public health measure for mass immunization of populations threatened with cholera. The Panel recommends that the major efforts to control cholera comprise those of a sanitary nature and, in addition, include development of surveillance systems and provision of adequate facilities for diagnosis and treatment. Vaccine at present can be recommended for individuals who may visit countries that still require evidence of immunization beyond the current requirements of International Health Regulations. Cholera vaccine may also be prescribed as a secondary measure in the prevention of cholera in special circumstances for individuals or groups who need or may desire an additional measure of protection beyond that provided by sensible precautions in consumption of food and drink.

Basis for Classification

Because of the limited efficacy of cholera vaccine and the need for field trials in foreign lands for proof of efficacy, the Panel considered that the mouse protection test, which has been well-correlated with efficacy, and fidelity to methods of well-established vaccine production are all that can be relied upon as a basis for classification.

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SPECIFIC PRODUCT REVIEWS

Cholera Vaccine Manufactured by Eli Lilly and Company

1. *Description.* The vaccine is a suspension of killed vibrio organisms prepared from the Inaba and Ogawa (equal parts) serotypes of *Vibrio cholerae.* The organisms are grown on nutrient agar, suspended in isotonic sodium chloride solution, and killed with 0.5 percent phenol, which serves as the preservative. The vaccine is standardized to contain 8,000 million organisms per mL. Total nitrogen content of the final vaccine does not exceed 0.05 mg nondialyzable nitrogen per dose.

2. *Labeling*—a. *Recommended use/indications.* The vaccine is recommended for active immunization against cholera. The dose is a single 0.5 mL injection subcutaneously or intramuscularly, but a second injection of 1 mL, presumably 1 month or more later, is recommended when insanitary conditions may be encountered. Booster doses of 0.5 mL are indicated every 6 months if protection is needed. A reduced dosage schedule is recommended for children 5 to 9 years and a further reduction for children of 6 months to 4 years of age.

b. *Contraindications.* Vaccine should not be given during acute illness, convalescence from surgery or trauma, or in other conditions that would depress the immune response. The manufacturer cautions against simultaneous use of steroids, etc., during immunization and comments on their danger in the presence of exposure to infectious disease.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* The submission (Ref. 1) cites various articles on the effectiveness of cholera vaccine in field trials. It fails to note that at least one of these trials was actually conducted with Eli Lilly and Company's cholera vaccine. The trial in question gave some of the best protection results observed to date.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* A large number of doses have been distributed in the last 5 years with only 11 complaints, 3 of which are presumably irrelevant.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore, within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* Despite the generally modest evidence regarding any specific cholera vaccine, as well as cholera vaccines in general, this product is of relatively high acceptability when circumstances indicate its use. The label points out the shortcomings of cholera vaccine and is generally adequate. However, the importance of hygienic measures to control this disease should be pointed out in the package insert, which should also note the recent evidence suggesting that the second dose may be reduced to 0.5 mL. The lengthy discussion on corticosteroids in the face of infectious diseases is execssive and should be shortened.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Cholera Vaccine Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Cholera vaccine is a bivalent mixture of *Vibrio cholerae* containing Ogawa and Inaba serotypes, each at a concentration of 4×10^9 cells per mL (total count 8×10^9 per mL). Lederle Laboratories Division's vaccine contains organisms grown in casein hydrolysate broth and killed and preserved with 0.45 percent phenol.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against cholera. The recommended dosage consists of 0.5 mL and 1.0 mL injections 4 weeks apart with reimmunization every 6 months. No provision is made for reduced dosage for children.

b. *Contraindications.* Not recommended for use in the presence of acute infections.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No specific data on immunogenicity of this product in man was provided. This particular product has not been employed in a controlled field trial, but is similar in potency to products which have been so evaluated and found to give modest protection (±50 to 70 percent) for 3 to 6 months.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Data from the manufacturer's complaint files revealed a very low rate of reaction complaints, all of a relatively minor nature.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore, within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

d. *Labeling.* The labeling needs to be revised to correct one minor inaccuracy in that the United States Public Health Service no longer requires vaccination of travelers entering the United States

from infected areas. In fact, cholera vaccine is no longer required by International Health Regulations, but a number of nations still unilaterally require it.

4. *Critique.* A field trial would be impractical for obvious reasons as previously discussed in this Report. Vibriocidal antibody levels in recipients could be determined, but would be hard to interpret and would inevitably be seen with vaccines meeting U.S. standards of potency. The labeling fairly states the limited expectation for efficacy of such a product.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Cholera Vaccine Manufactured by Merck Sharp & Dohme, Division of Merck & Co., Inc.

1. *Description.* The manufacturer has provided very little material except to say that it contains 4 billion cells each of killed whole bacteria of the Inaba and Ogawa strains per mL. The diluent is physiological saline with 0.5 percent phenol.

2. *Labeling*—a. *Recommended use/indications.* No package insert is provided. However, the label states that 2 doses at 7- to 10-day intervals given subcutaneously are recommended, the first being 0.5 mL and the second 1.0 mL.

b. *Contraindications.* None is mentioned.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* None is described.

(2) *Human.* None is described except reference to other studies. However, in the submission (Ref. 2) there is one reference to McBean (Ref. 3), in which a few patients were given this preparation both subcutaneously and intradermally to compare the two routes. Apparently titers were satisfactory.

b. *Safety*—(1) *Animal.* This submission states that the bulk vaccine and the final product meet Federal requirements.

(2) *Human.* No evidence is provided.

c. *Benefit/risk ratio.* The benefit-to-risk assessment for this product cannot be determined because of insufficient information.

4. *Critique.* This submission is incomplete. Little or no information regarding efficacy is supplied, and the submission regarding animal safety is minimal. There are no data submitted regarding human safety. Apparently this manufacturer is simply retaining its license but the product does not appear to be marketed.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIC and that the appropriate license be revoked for administrative reasons because this product is not marketed and there are insufficient data on labeling, safety, and effectiveness.

Cholera Vaccine Manufactured by Merrell-National Laboratories, Division of Richardson-Merrell, Inc.

1. *Description.* Each mL of vaccine contains 8×10^9 killed *Vibrio cholerae*, 4×10^9 Ogawa and 4×10^9 Inaba strain, suspended in isotonic sodium chloride solution. The organisms are grown on agar and killed and preserved with 0.5 percent phenol.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against cholera. It is pointed out that immunization is mandatory for travel in many parts of the world. However, none of the shortcomings of cholera vaccine is mentioned.

(1) *Adults.* Initial injection of 0.5 mL; a second injection of 1.0 mL given 1 week to 1 month or more later. Booster injections: 0.5 mL every 6 months while danger of infection exists.

(2) *Children.* Two injections given 1 week to 1 month apart, in the following dosage according to age: 6 months to 4 years: 0.1 mL, 0.3 mL; 5 to 9 years: 0.3 mL, 0.5 mL; and 10 years and over: adult schedule.

(3) *Booster injections.* Give the same amount as the first dose indicated above every 6 months while danger of infection exists.

b. *Contraindications.* It is stated "None known." Adverse reactions are mentioned.

3. *Analysis*—a. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Referral (Ref. 4) to the general literature only, with no information specifically for this product.

b. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* One study by Verway (Ref. 5) compares vibriocidal antibody responses among volunteers given either Cholera Research Laboratory vaccine (apparently manufactured by Eli Lilly and Company) or a vaccine from the National Drug Company. Since the National Drug Company's product is now the Merrell-National Laboratories' product, there are data in support of human immunogenicity for this product.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of the product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* The labeling could be improved by mentioning that only one injection is required for international travel, although two injections may give somewhat better protection. The short duration of protection from cholera vaccine is not mentioned, although the need for booster injections is pointed out. Under contraindications it is merely stated that none are known, whereas the vaccine probably should not be given during acute illnesses and in persons who have previously experienced severe reactions to the vaccine.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

Cholera Vaccine Manufactured by Wyeth Laboratories, Inc.

1. *Description.* Each 1 mL of the vaccine contains not more than 4×10^9 *Vibrio cholera*, serotype Inaba, not more than 4×10^9 *Vibrio cholera*, serotype Ogawa which has been on trypticase soy agar containing pancreatic digest of casein, soy poptone, and sodium chloride. The organisms are removed from the agar surface, suspended in 0.02 molar phosphate buffered saline, and phenol added to a concentration of 0.5 percent.

2. *Labeling*—a. *Recommended use/indications.* This product is recommended for active immunization against cholera. The recommended dose and intervals between doses are clearly delineated in the labeling.

b. *Contraindications.* Intercurrent active infection is listed as a contraindication to vaccination.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Nine controlled studies have been carried out in the Phillipines, Bangladesh, and in India (Ref. 6). Vaccines of this type have shown from 39 to 93 percent protection. Mosley (Ref. 7) has demonstrated that a doubling of the mean vibriocidal antibody titer by active immunization was associated with a 50 to 60 percent reduction of the cholera case rate. It is not clear whether or not a Wyeth Laboratory preparation, per se, was used in any of these trials.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* Local reactions are reported to be common; in addition, some patients experience malaise and

fever. No specific data, however, are provided in the submission (Ref. 8) with regard to the safety of Wyeth Laboratories' cholera vaccine.

c. *Benefit/risk ratio.* The benefits for most recipients (especially travelers) are minor, but the risk factor is very slight. Therefore within the general limitations and expectations of cholera vaccine, the benefit-to-risk assessment of this product is satisfactory in those instances in which vaccine use is indicated.

4. *Critique.* Within the general limitations of presently available killed/whole bacterial cell cholera vaccines as discussed in the generic statement, this product is acceptably safe and effective. The labeling, while presently satisfactory and in conformity with national recommendations, should be revised to reflect the recommendations of the Panel as found in the Generic Statement on Labeling.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued with the stipulation that labeling be revised in accordance with the recommendations of this Report.

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Generic Statement

Plague Vaccine

Plague is an acute infectious disease caused by a gram-negative bacillus, *Yersinia pestis,* which has its natural reservoir in wild rodents. In its classical form usual features include lymphadenitis and septicemia. Often toxemia, high fever, petechial hemorrhages, and shock are concomitant features. There are three clinical forms: bubonic, primary septicemic, and primary pneumonic. Untreated bubonic plague has a case fatality rate of about 50 percent, while untreated primary septicemic or pneumonic plague is almost uniformly fatal. Sylvatic plague exists in the Western one-third of the United States, but cases in man are sporadic (20 cases were reported in the United States in 1975) and routine immunization of general population has not been recommended.

Description and Production

Plague vaccine U.S.P. is produced from *Yersinia pestis* strain 195/P, which is grown on E medium and the harvested organisms are killed by addition of 37 percent formaldehyde (final concentration, 0.5 percent formalin). Phenol is added to a final concentration of 0.5 percent as a preservative. The vaccine contains trace amounts of media constituents but no detectable blood group substances.

Indications and Contraindications

Immunization is recommended for those persons who must be in known plague-endemic areas, such as Laos, Cambodia, and Vietnam and certain areas in the Western Hemisphere. In addition, antiplague immunization seems appropriate for selected groups such as laboratory workers, field personnel and epidemiologists who are involved in plague research and/or study. Despite its reactogenicity, when indicated, there apparently are no absolute contraindications.

Safety

Plague vaccine produces both local and systemic reactions. Local reactions consist of edema and/or induration at the site of inoculation. Such reactions may demonstrate a wheal and flare response and may temporarily limit the use of the involved extremity. Systemic reactions vary from malaise, mild headache, and generalized muscular aches to anaphylactoid responses.

In carefully observed subjects (2,688 injections of E medium vaccine into 523 individuals) (Ref. 1), local reactions occurred in 11 to 24 percent of individuals while systemic reactions occurred in 4 to 10 percent. Urticarial responses occurred in 0.07 percent. With reduction in booster dosage from 0.5 mL to 0.25 mL, a 65 to 70 percent reduction in systemic and local reactions ensued without apparent loss of immunogenicity.

Efficacy

The efficacy of killed plague vaccine in humans has not been defined in well-designed controlled field trials. However, the efficacy of plague vaccine (E medium) has been demonstrated to the satisfaction of the Panel by reviewing the experience of U.S. military personnel in Southeast Asia from 1963 to 1972 (Refs. 2 and 3). This latter experience briefly summarized is as follows: (1) A rate of one case of diagnosed plague infection per million man-years of exposure occurred among vaccinated Americans operating in Vietnam; (2) thousands of Vietnamese (approximately 5,000 cases per year per 15 million population, i.e., 333 cases per million man-years) contracted plague during this period with confirmation in many and with frequent fatilities; and (3) Americans frequently contracted murine typhus caused by *Rickettsia mooseri,* an agent which is carried and transmitted in Vietnam by the same flea/rodent hosts as *Yersinia pestis* (the Oriental rat flea *Xenopsylla cheopis* and domestic rats, *Rattus species*). In one study, 12 percent of American patients with proven murine typhus had serological evidence suggesting that they were concomitantly infected with *Yersinia pestis,* but none developed clinical evidence of bubonic plague.

One factor that could not be documented from the available data derived from the Vietnam experience is what proportion of the U.S. personnel had received no more than three doses of plague vaccine prior to their field service and potential exposure. A reasonable estimate would be that approximately 75 percent of personnel fell into this category. A second variable that could not be documented was the extent of and criteria for use of antibiotics such as tetracyclines since many febrile illnesses were treated empirically with broad-spectrum antibiotics.

Despite evidence that strongly suggests that plague vaccine is effective, an optimal vaccination schedule remains to be determined. The administration of booster doses at 3-month intervals as recommended by the manufacturer or even at 6-month intervals as carried out by the U.S. military has many drawbacks, particularly in the context of the reaction rates. In addition, recent studies suggest that such frequent injections are unnecessary.

Investigators at the U.S. Army Medical Research Institute of Infectious Diseases and at the Walter Reed Army Institute of Research have shown that